



Diagnostic Accuracy of Myocardial Perfusion Imaging With CZT Technology

Systemic Review and Meta-Analysis of Comparison With Invasive Coronary Angiography

Francesco Nudi, MD,^{a,b,c} Ami E. Iskandrian, MD,^d Orazio Schillaci, MD,^e Mariangela Peruzzi, MD, PhD,^f Giacomo Frati, MD, MSc,^{f,g} Giuseppe Biondi-Zoccai, MD, MSTAT^{f,g}

ABSTRACT

OBJECTIVES This study sought to summarize the evidence on stress myocardial perfusion imaging (MPI) using cadmium-zinc-telluride (CZT) technology for the diagnosis of obstructive coronary artery disease (CAD). The CZT cameras are newly introduced, and comparative data with the conventional Anger technology (Anger-MPI) are lacking.

BACKGROUND The diagnostic accuracy of Anger-MPI for detection of angiographically significant CAD is well established; however, less evidence is available on the diagnostic accuracy of CZT-MPI.

METHODS Clinical studies comparing CZT-MPI and invasive coronary angiography were systematically searched and abstracted. Calculations of diagnostic accuracy, including sensitivity, specificity, likelihood ratios, and diagnostic odds ratio, were obtained with fixed and random effects, reporting point estimates and 95% confidence intervals.

RESULTS Based on our search, a total of 16 studies (N = 2,092) were included. The sensitivity of CZT-MPI was 0.84 (95% confidence interval [CI]: 0.78 to 0.89), whereas the specificity of 0.69 (95% CI: 0.62 to 0.76) was significantly reduced. The positive likelihood ratio was 2.73 (95% CI: 2.21 to 3.39), the negative likelihood ratio was 0.24 (95% CI: 0.17 to 0.31), and the diagnostic odds ratio was 11.93 (95% CI: 7.84 to 17.42). At subgroup and meta-regression analyses, the diagnostic accuracy between D-SPECT and Discovery cameras was similar (p = 0.711) and not impacted upon by smaller sample size studies (p = 0.573).

CONCLUSIONS CZT-MPI has satisfactory sensitivity for angiographically significant CAD, but its suboptimal specificity warrants further development and research. (J Am Coll Cardiol Img 2017;10:787-94) © 2017 by the American College of Cardiology Foundation.

Radionuclide myocardial perfusion imaging (MPI) is one of the most common stress imaging procedures performed and is a central tool in the diagnosis and assessment of risk in patients with stable ischemic heart disease (1). Stress MPI provides important information on ischemia, scar, and left ventricular volumes and ejection fraction (2). Anger camera technology has been the

workhorse of stress MPI for decades. More recently, cadmium-zinc-telluride (CZT) cameras were introduced into clinical practice by 2 vendors (3-10). This technology is now available for clinical application with anecdotal reports on suboptimal image quality due to patient motion, incorrect positioning, or obesity, which potentially may lead to reduced specificity (11-13).

From the ^aService of Hybrid Cardio Imaging, Madonna della Fiducia Clinic, Rome, Italy; ^bOstia Radiologica, Ostia, Italy; ^cEtisan, Rome, Italy; ^dDivision of Cardiovascular Disease, University of Alabama at Birmingham, Alabama; ^eDepartment of Nuclear Medicine, Tor Vergata University, Rome, Italy; ^fDepartment of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; and the ^gDepartment of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy. This work was supported by Etisan, Rome, Italy. Dr. Iskandrian has served as a consultant to Lantheus Pharma and GE on Imaging Committee for phase 3 trial with I-123 MIBG; and has served as a scientific advisor for Rapid scan Pharma. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CZT = cadmium-zinc-telluride

MPI = myocardial perfusion
imaging

SPECT = single-photon
emission computed
tomography

Tc = technetium

The primary aim of this report was to evaluate the current evidence on the diagnostic accuracy of CZT-MPI. Thus, we conducted a systematic review and meta-analysis of the available published literature (14-16).

METHODS

STUDY DESIGN. This review was prepared in keeping with The Cochrane Collaboration recommendations (14,17) and the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Online Table 1S) (18).

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SEARCH. PubMed was searched for studies reporting on MPI using CZT-single-photon emission computed tomography (SPECT) with the following highly sensitive strategy: “(czt OR (cadmium-zinc-telluride) OR (cadmium AND zinc AND telluride) OR (alcyone OR dspect OR d-spect)) AND myocardial AND (imaging OR scintigraphy).” The Cochrane Library was also searched with the string “cadmium AND zinc AND telluride AND myocardial.” References of shortlisted studies were checked for additional studies. Citations were first screened at the title/abstract level and then retrieved as full texts if potentially pertinent. Full texts were then appraised formally according to explicit selection criteria. No language restriction was enforced.

SELECTION, ABSTRACTION, AND APPRAISAL. We included all studies that reported at least 5 patients in

whom both MPI and coronary angiography had been performed within a clinically reasonable time frame and provided adequate details to allow extraction of actual information for true positives, true negatives, false positives, and false negatives. No formal exclusion criterion was enforced, except for duplicate reports.

Several design, baseline, procedural, and outcome features were extracted, including body mass index (BMI) and prevalence of obesity, as well as type of CZT-MPI and acquisition protocol (e.g., stress/rest). Study validity was appraised using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 checklist (19).

STATISTICAL ANALYSIS. Continuous variables are given as medians and categorical variables as percentages. Diagnostic accuracy was described through sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio, with summary estimates (and 95% confidence intervals) and corresponding p values for effect [p_{effect}] with an univariate model (14,20,21).

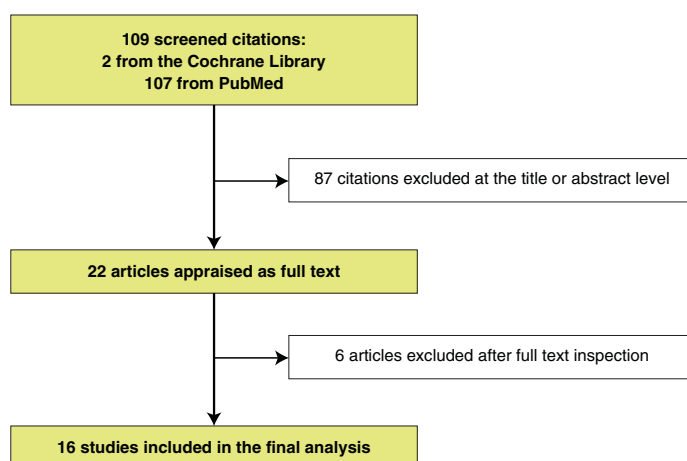
Our primary analysis used Reitsma bivariate and proportional hazard models, which are less prone to bias given the correlation between sensitivity and false-positive rate ($1 - \text{specificity}$) that is typical of diagnostic studies (14,20,21). The presence of a threshold effect with potentially biasing effects was analyzed with the Spearman correlation test (14).

We also used meta-regression utilizing a Reitsma bivariate model for sensitivity and false-positive rate, as well as univariate analysis for calculation of diagnostic odds ratios. Statistical heterogeneity and inconsistency were appraised with chi-square test, Cochran Q test, Higgins I^2 , and tau², reporting corresponding p values for heterogeneity (p_{het}). Several subgroups analyses were conducted to explore potential sources of heterogeneity. Small study effects were evaluated graphically with funnel plot inspection and analytically with Deeks and Egger regression tests (22). All calculations were performed using Meta-Disc 1.4 (Ramón y Cajal Hospital, Madrid, Spain), Stata 13 (StataCorp, College Station, Texas), and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) (23,24).

RESULTS

SYSTEMATIC REVIEW. From among 109 citations, 22 were identified and reviewed for relevance to our primary study aim. We then identified a total of 16 studies eligible for inclusion, encompassing a total of 2,092 patients (median sample size: 110 patients) (Figure 1) (8,25-39). In particular, Duvall et al. (29,30) reported

FIGURE 1 Review Flowchart



Profile of the reviewing process for the systematic review.

TABLE 1 Key Features of Included Studies (All Studies Were Reported in English Scientific Journals)

First Author (Year) (Ref. #)	Setting	Study Type	CZT-SPECT	N	Age (yrs)	Men	DM	Obesity	BMI (kg/m ²)
Ben-Haim (2010) (26)	Single center	Prospective observational	D-SPECT	5	65	64%	36%	NA	26
Duvall (2011) (29)	Single center	Retrospective clinical	Discovery NM 530c	230	64	69%	40%	NA	28
Fiechter (2011) (8)	Single center	Retrospective clinical	Discovery NM/CT 570c	66	63	79%	36%	35%	28
Gimelli (2012) (31)	Single center	Prospective observational	Discovery NM 530c	137	61	74%	28%	10%	NA
Ben-Haim (2014) (27)	Single center	Retrospective clinical	D-SPECT	19	62	49%	39%	100%	36
Chowdhury (2014) (28)	Single center	Retrospective clinical	Discovery NM 530c	165	63	52%	16%	NA	NA
Duvall (2014) (30)	Single center	Retrospective clinical	Discovery NM 530c	115	60	41%	31%	NA	29
Goto (2014) (32)	Multicenter	Retrospective clinical	Discovery NM 530c	322	69	73%	41%	NA	25
Mouden (2014) (34)	Single center	Prospective observational	Discovery NM/CT 570c	100	66	50%	31%	NA	29
Nishiyama (2014) (36)	Single center	Retrospective clinical	Discovery NM 530c	76	69	63%	42%	NA	24
Barone-Rochette (2015) (25)	Single center	Retrospective clinical	Discovery NM 530c	104	65	70%	38%	32%	27
Liu (2015) (33)	Single center	Retrospective clinical	Discovery NM 530c	211	59	NA	29%	NA	26
Nakazato (2015) (35)	Multicenter	Retrospective clinical	D-SPECT	67	56	50%	41%	100%	42
Perrin (2015) (37)	Single center	Retrospective clinical	D-SPECT	149	62	80%	31%	30%	28
Shiraishi (2015) (39)	Single center	Retrospective clinical	Discovery NM 530c	55	75	25%	40%	NA	24
Sharir (2016) (38)	Single center	Retrospective clinical	Discovery NM 530c	271	61	69%	28%	NA	27

TABLE 1 Continued

First Author (Year) (Ref. #)	Prior CAD	Cohort	Index test	Comparator
Ben-Haim (2010) (26)	84%	Stable CAD	Stress Tc/rest Tl dual-isotope MPI	Qualitative angiographic analysis (50% cutoff)-ICA within 3 months
Duvall (2011) (29)	53%	Stable CAD	Stress-only, rest/stress, or stress/rest Tl or Tc MPI	Qualitative angiographic analysis (70% cutoff)-ICA within 2 months
Fiechter (2011) (8)	NA	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (50% cutoff)-ICA within 3 months
Gimelli (2012) (31)	NA	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (50% cutoff)-ICA within 1 months
Ben-Haim (2014) (27)	35%	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (70% cutoff)-ICA within 3 months
Chowdhury (2014) (28)	33%	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (70% cutoff)-ICA within 2 months
Duvall (2014) (30)	16%	Acute chest pain	Stress-only, rest/stress, or stress/rest Tc MPI	Qualitative angiographic analysis (unspecified cutoff)-ICA up to 18 months after MPI
Goto (2014) (32)	NA	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (75% cutoff)-ICA within 2 months
Mouden (2014) (34)	NA	Stable CAD	Stress/rest Tc MPI	Fractional flow reserve (0.75 cutoff) within 1 day
Nishiyama (2014) (36)	NA	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (50% cutoff)-ICA within 3 months
Barone-Rochette (2015) (25)	51%	Stable CAD (no prior CABG)	Stress Tl/rest Tc dual-isotope MPI	Quantitative angiographic analysis (70% cutoff)-ICA within 3 months
Liu (2015) (33)	NA	Stable CAD	Stress/rest Tl MPI	Qualitative angiographic analysis (70% cutoff)-ICA within 6 months
Nakazato (2015) (35)	NA	Stable CAD	Rest/stress or stress/rest Tl or Tc MPI	Qualitative angiographic analysis (50% cutoff)-ICA within 2 months
Perrin (2015) (37)	55%	Stable CAD	Stress-only or stress/rest Tc MPI	Quantitative angiographic analysis (50% cutoff)-ICA within 3 months
Shiraishi (2015) (39)	NA	Stable CAD	Stress/rest Tl MPI	Qualitative angiographic analysis (75% cutoff)-ICA within 1 months
Sharir (2016) (38)	NA	Stable CAD	Stress/rest Tc MPI	Qualitative angiographic analysis (70% cutoff)-ICA within 2 months

BMI = body mass index; CAD = coronary artery disease; CZT-SPECT = cadmium-zinc-telluride single-photon emission computed tomography; DM = diabetes mellitus; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; NA = not available or applicable; Pts = patients; Tc = Technetium-99m; Tl = thallium-201.

on 2 different patient cohorts from the same institution, and the report by Gimelli et al. (31) was selected as the most recent from the corresponding institution. Study quality overall was high despite the pragmatic features of most studies, which were typically characterized by a potential selection bias for coronary angiography (Online Table 2S). The studies were published between 2010 and 2016, and were mostly single-center retrospective observational reports (Table 1). Median age of patients was 63 years. Most series included men and overweight-obese patients, with the obese patients being the sole focus of enrollment in 2 studies. Moreover, diabetics accounted for a sizeable

proportion of enrolled patients (average 34% of subjects), and nearly one-half of the patients had prior coronary artery disease (CAD) (Table 1, Online Table 3S). The majority of reported patients had stable CAD (either suspected or known), except for patients included in the study by Duvall et al. (30), who were evaluated for acute chest pain. A stress/rest protocol was used in all studies, and dual isotope administration was used in 2 (Online Table 4S). The Discovery NM 530c or Discovery NM/CT 570c camera (with Alcyone technology, GE Healthcare, Haifa, Israel) was used in 12 studies, whereas the D-SPECT (Spectrum Dynamics, Palo Alto, California) was used in the remaining

TABLE 2 Study-Level Features of Diagnostic Accuracy

First Author (Year) (Ref. #)	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	Diagnostic Odds Ratio
Ben-Haim (2010) (26)	4	0	1	0	0.90	0.25	1.20	0.40	3.00
Duvall (2011) (29)	121	38	65	6	0.95	0.37	1.51	0.14	10.99
Fiechter (2011) (8)	44	10	5	7	0.86	0.66	2.49	0.22	11.33
Gimelli (2012) (31)	103	14	10	10	0.91	0.58	2.16	0.16	13.61
Ben-Haim (2014) (27)	7	10	1	1	0.83	0.88	6.67	0.19	35.00
Chowdhury (2014) (28)	74	61	16	14	0.84	0.79	3.96	0.21	19.15
Duvall (2014) (30)	31	37	23	24	0.56	0.61	14.60	0.71	2.05
Goto (2014) (32)	51	187	73	11	0.82	0.72	2.90	0.25	11.42
Mouden (2014) (34)	12	61	19	8	0.60	0.76	2.47	0.53	4.64
Nishiyama (2014) (36)	46	18	4	8	0.85	0.80	4.32	0.19	22.49
Barone-Rochette (2015) (25)	73	13	13	5	0.93	0.50	1.86	0.14	13.36
Liu (2015) (33)	27	130	46	8	0.76	0.74	2.91	0.32	9.08
Nakazato (2015) (35)	31	23	5	8	0.79	0.81	4.15	0.26	15.83
Perrin (2015) (37)	93	26	17	13	0.87	0.60	2.20	0.21	10.49
Shiraishi (2015) (39)	12	32	9	2	0.83	0.77	3.68	0.22	17.11
Sharir (2016) (38)	122	111	23	15	0.89	0.83	5.10	0.14	37.50

4 studies. Acquisition with both Anger and CZT cameras was performed only in the study by Ben-Haim et al. (26).

Positive MPI was defined based on stress-only MPI in 9 studies and using stress and rest MPI in 7 studies. Significant CAD was defined using qualitative coronary angiography in 13 studies, quantitative coronary angiography in 2 studies, and invasive fractional flow reserve in 1 study. Definitions of significant stenosis were heterogeneous across the studies. Specifically, 8 studies used $\geq 70\%$ to 75% diameter stenosis, 6 studies used $\geq 50\%$ stenosis, 1 study did not specify an explicit cutoff, and 1 study used ≤ 0.75 fractional flow reserve threshold for significant CAD. Radiation exposure was reported in 5 studies. Barone-Rochette et al. (25) reported an average radiation exposure of 12 mSv from dual-isotope MPI (rest thallium-201 and stress technetium [Tc]-99m). Fiechter et al. (8) reported an average radiation exposure of 10 mSv using Tc-99m (with obesity in nearly one-third of patients). Duvall et al. (30) reported an average radiation exposure of 32 mSv using Tc-99m in a largely obese

patient subset with an average BMI of 29 kg/m². By comparison, lower radiation doses were reported in populations with a lower prevalence of obesity, such as those reported by Gimelli et al. (31) (average dose: 6 mSv) and Perrin et al. (37) (average dose: 5 mSv).

Image acquisition was stress/rest in 12 studies, and rest/stress and stress-only were used in the other studies. Image acquisition was obtained in the prone position only or in the prone and supine positions in 7 studies.

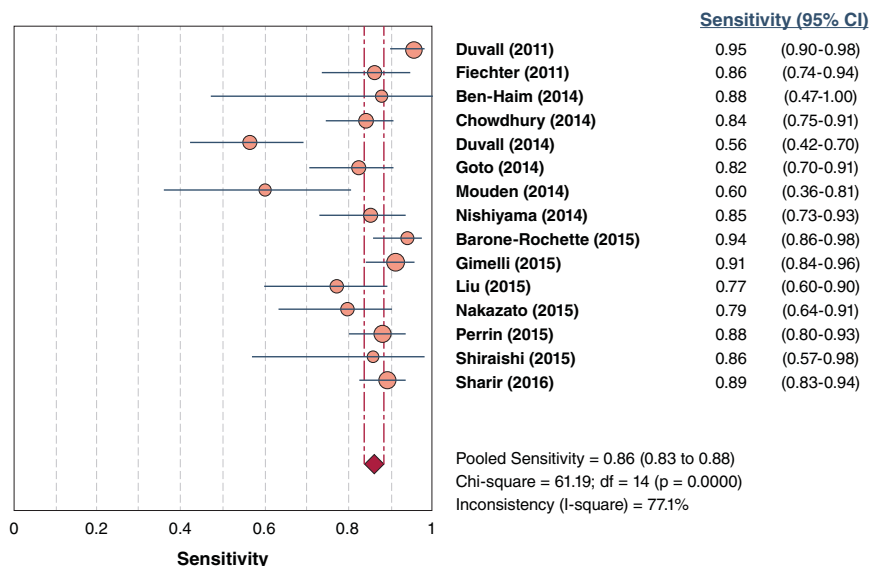
DIAGNOSTIC ACCURACY. Pooled analysis with a random effects bivariate model yielded the following calculations: sensitivity = 0.84 (0.78 to 0.89; $p_{\text{effect}} < 0.001$; $p_{\text{het}} < 0.001$; $I^2 = 76\%$), specificity = 0.69 (0.62 to 0.76; $p_{\text{effect}} < 0.001$; $p_{\text{het}} < 0.001$; $I^2 = 82\%$), positive likelihood ratio = 2.73 (2.21 to 3.39; $p_{\text{effect}} < 0.001$; $p_{\text{het}} < 0.001$; $I^2 = 83\%$), negative likelihood ratio = 0.24 (0.17 to 0.31; $p_{\text{effect}} < 0.001$; $p_{\text{het}} < 0.001$; $I^2 = 74\%$), and diagnostic odds ratio = 11.93 (7.84 to 17.42; $p_{\text{effect}} < 0.001$; $p_{\text{het}} < 0.001$; $I^2 = 64\%$) (Tables 2 and 3, Figures 2 and 3, Online Figure 1S). Findings were mostly similar even though different models were used, including the univariate random effects model and the univariate fixed effect model (Online Figures 2S, 3S, and 4S).

THRESHOLD, PUBLICATION BIAS, META-REGRESSION, AND ANCILLARY ANALYSES. Several additional analyses were conducted to explore potential effect modifiers (Online Tables 5S and 6S). We found no evidence of threshold effect by computing the Spearman correlation test between sensitivity and false positive rate ($p = 0.201$) (20,21). Similarly, tests for publication bias were not significant ($p = 0.651$ with Deeks test and $p = 0.573$ with Egger tests).

TABLE 3 Inferential Pooled Analysis for Diagnostic Accuracy

	Reitsma Model (Random Effects)	Univariate Analysis (Fixed Effect)
Sensitivity	0.84 (0.78–0.89), $p_{\text{effect}} < 0.001$	0.86 (0.84–0.88), $p_{\text{effect}} < 0.001$
Specificity	0.69 (0.62–0.76), $p_{\text{effect}} < 0.001$	0.70 (0.67–0.73), $p_{\text{effect}} < 0.001$
Positive likelihood ratio	2.73 (2.21–3.39), $p_{\text{effect}} < 0.001$	2.70 (2.09–3.48), $p_{\text{effect}} < 0.001$
Negative likelihood ratio	0.24 (0.17–0.31), $p_{\text{effect}} < 0.001$	0.23 (0.16–0.32), $p_{\text{effect}} < 0.001$
Diagnostic odds ratio	11.93 (7.84–17.42), $p_{\text{effect}} < 0.001$	12.59 (8.11–19.54), $p_{\text{effect}} < 0.001$
Values are point estimate (95% confidence interval).		

FIGURE 2 Forest Plot of Univariate Analysis for Sensitivity

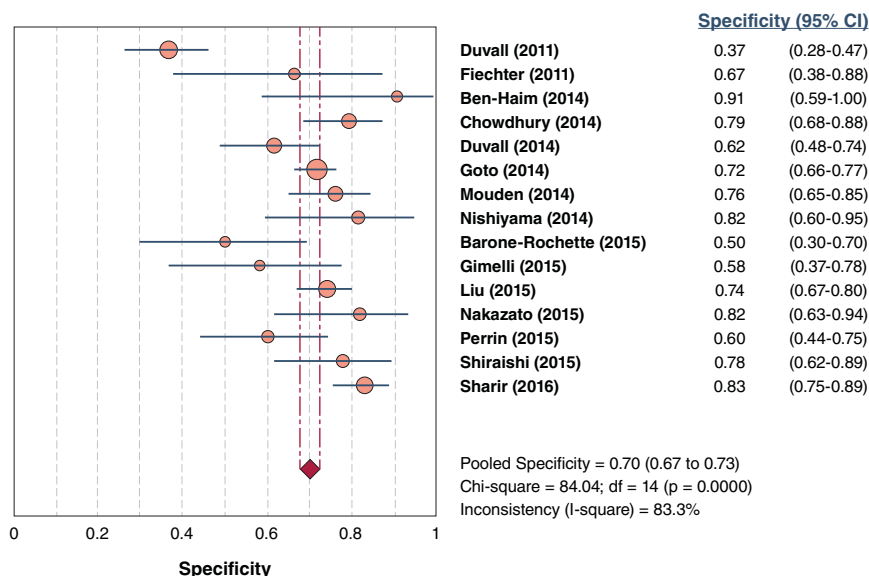


Heterogeneity was appraised using the chi-square test, with corresponding degrees of freedom (df) and p value. CI = confidence interval.

(Online Figure 5S). Meta-regression was used to explore for potential effect moderators, including year of publication, patient characteristics (age, BMI, and diabetes), definition of positive MPI, and type of CZT-MPI camera. The meta-regression findings

identified several parameters associated with improved diagnostic specificity, including recentness of publication (p = 0.005) as well as application of quantitative (p = 0.018) or semiquantitative segmental scoring methods (p = 0.013) for MPI

FIGURE 3 Forest Plot of Univariate Analysis for Specificity



Heterogeneity was appraised using the chi-square test, with corresponding degrees of freedom (df) and p value. CI = confidence interval.

interpretation. Additional plots appraising the goodness of fit of the model and normality assumption, and exploring the impact of the most influential studies and the presence of outlying studies are available in the [Online Appendix](#), together with additional subgroup analyses ([Online Figures 6S and 7S](#)).

DISCUSSION

Noninvasive stress MPI for evaluation of suspected ischemia is the mainstay for management of patients with suspected or established CAD (1,2). The evidence base is robust and supports the clinical utility of stress MPI in the diagnostic, prognostic, and therapeutic work-up of CAD. The conventional Anger cameras for SPECT-MPI have been in existence for decades (3). More recently, CZT cameras have been introduced as an alternative to the conventional Anger technology. These cameras have been advocated as an effective means to reduce radiation exposure and acquisition time for patients undergoing MPI (4). Our analysis focused on a systematic review and meta-analysis of the diagnostic accuracy of the new CZT cameras.

Our main results showed that CZT-MPI has satisfactory sensitivity for significant CAD (84%), results comparable to prior summary reports using conventional Anger technology. However, the summary diagnostic specificity for CZT-MPI was reduced to 69% and revealed false-positive findings in nearly one-third of patients. This high rate of false-positive findings may reflect issues related to breast attenuation or obesity, which was prevalent in several series.

The evidence on the diagnostic performance of Anger-SPECT is well established, with current data yielding estimates for sensitivity ranging between 0.82 and 0.91, and for specificity between 0.70 to 0.90, depending on clinical history and chosen cutoff for significant CAD (40). Prior comparative data in patients undergoing both CZT-SPECT and Anger-SPECT have shown that both imaging methods have reasonable concordance measurements, especially when obese patients are excluded (13). In addition, CZT-MPI, with its upright imaging, is generally more comfortable for patients. However, the ability to image upright and the tendency for imaging of a mainly obese patient subgroup may result in reduced diagnostic specificity, as supported by our meta-analytic findings.

Heterogeneity and inconsistency between individual studies was substantial, with the following significant effect modifiers: recentness of publication, use of segmental or quantitative score, and application of stress-only MPI. Currently, 2 types of CZT-MPI cameras are available for clinical application including Alcyone technology (Discovery NM 530c

and Discovery NM/CT 570c) with multi-pinhole collimation and D-SPECT with parallel-hole collimation (4-11). Our analysis did not identify significant differences based on the type of CZT-MPI camera used in studies in the published literature.

STUDY LIMITATIONS. This work has several limitations, including those inherent to systematic reviews and meta-analyses of diagnostic test accuracy studies. The heterogeneity in study features, patients, protocols, cameras, and definitions may lead to inconsistent estimates. Given the study-level design and the specifics of included studies, no subgroup analysis focusing on gender was possible. Finally, image quality was inconsistently reported and thus could not be appraised in detail.

CONCLUSIONS

MPI with the novel CZT technology has relatively comparable diagnostic sensitivity for angiographically-significant CAD to Anger-SPECT. The reduced diagnostic specificity, which resulted in a high rate of false-positive findings with CZT-MPI, warrants further research, particularly as it relates to imaging of obese patients.

ADDRESS FOR CORRESPONDENCE: Dr. Giuseppe Biondi-Zoccai, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Corso della Repubblica 79, 04100 Latina, Italy. E-mail: giuseppe.biondizoccai@uniroma1.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The diagnostic accuracy of MPI with conventional Anger technology to detect CAD is well established, but the role of the novel CZT technology, which can significantly reduce radiation exposure, is not clearly defined. A comprehensive systematic review and meta-analysis showed that MPI with CZT has favorable sensitivity in comparison to invasive coronary angiography. However, a reduced diagnostic specificity was reported.

TRANSLATIONAL OUTLOOK: MPI with CZT has a promising role in the diagnostic work-up of suspected or established CAD, if additional development and research can identify strategies to improve diagnostic specificity. Further studies are required to appraise its diagnostic accuracy in comparison to other noninvasive imaging modalities, such as magnetic resonance imaging, and to gauge its role in risk stratification and to guide decision making in patients with CAD.

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APPENDIX For supplemental tables and figures, please see the online version of this article.